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Blood-brain barrier and retroviral infections

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Homeostasis in the central nervous system (CNS) is maintained by active interfaces between the bloodstream and the brain parenchyma. The blood-brain barrier (BBB) constitutes a selective filter for exchange of water, solutes, nutrients, and controls toxic compounds or pathogens entry. Some parasites, bacteria, and viruses have however developed various CNS invasion strategies, and can bypass the brain barriers. Concerning viruses, these strategies include transport along neural pathways, transcytosis, infection of the brain endothelial cells, breaching of the BBB, and passage of infected-leukocytes. Moreover, neurotropic viruses can alter BBB functions, thus compromising CNS homeostasis. Retroviruses have been associated to human neurological diseases: HIV (human immunodeficiency virus 1) can induce HIV-associated dementia, and HTLV-1 (human T lymphotropic virus 1) is the etiological factor of tropical spastic paraparesis/HTLV-1 associated myelopathy (TSP/HAM). The present review focuses on how the different retroviruses interact with this structure, bypass it and alter its functions.

Introduction

The Central Nervous System (CNS), which is composed of the brain and the spinal cord, is mainly isolated from the rest of the organism by blood/brain interfaces, including the Blood-Brain Barrier (BBB) and the Blood-Cerebrospinal Fluid (CSF) barrier. These barriers maintain the CNS homeostasis, by regulating ions, water and solutes exchanges, and protect it from toxic compounds or pathogens. However, several pathogens have developed invasion strategies of the CNS, bypassing these barriers.

Neurotropic viruses, i.e., viruses that are able to infect neural cells can be retrieved in several viral families, such as Herpesviridae, Paramyxoviridae, Rhabdoviridae, Picornaviridae, Retroviridae,[1] etc. They can gain access to the CNS by different routes: either they use the neural network and the axonal transport (rabies virus or herpes simplex virus type I, for example[2]), or they invade the CNS from the bloodstream (West Nile virus, for example[3]). The hematogenous route is the one usually used by the retroviruses.

Retroviruses are enveloped RNA viruses that have the unique property of transcribing RNA into DNA, and integrating their retroviral DNA into the chromosomal DNA of the host cell. Two human retroviruses have been recognized to be responsible for major CNS diseases: human immunodeficiency virus type 1 (HIV-1), which can be responsible of damages to the brain and the spinal cord during acquired immune deficiency syndrome (AIDS) and human T-cell lymphotropic virus type 1 (HTLV-1), which is responsible for a progressive neurodegenerative disease, the tropical spastic paraparesis/HTLV-1-associated myelopathy (TSP/HAM) in some HTLV-1 infected persons. Other retroviruses, from the Lentiviral subgroup, are also able to induce neurological syndromes in animals. The present review summarizes the main characteristics of the BBB, and the different interactions between retroviruses and this structure.

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Overview of the Blood-Brain Barrier

The brain is a highly perfused organ: it represents only 2% of body weight, but receives 15–20% of total cardiac output. The blood/CNS interfaces are diverse: they include the BBB, as well as the blood cerebrospinal fluid barrier, the blood retinal barrier, the blood nerve barrier and the blood labyrinth barrier.[4] The barrier properties are usually determined by the endothelium of brain microvessels, but both in choroid plexus and arachnoid the barrier is determined by an epithelium. The cerebral endothelium is the primary site of oxygen and nutrient exchanges.[5] In the brain, it is estimated that nearly every neuron, the core components of the nervous system, has its own microvessel,[6] underlining the critical relationship between the neuronal and vascular compartments. The combined surface area of these microvessels, depending on the anatomical region, ranges between 150 and 200 cm^2 g^{-1} tissue, with a total area for exchange in the brain about 12 m^2 for the average human adult.[7,8]

The neurological activity requires a strict cerebral homeostasis. With the exception of the circumventricular organs, which are regions of important exchanges between specialized neurons and

the blood stream, the homeostasis of the CNS is achieved by exquisite regulation of nutrients, solutes and water exchanges at blood/CNS interfaces.[9]

As BBB specificities and characteristics are mainly induced, maintained and/or interfered by cerebral vicinity, it is worth to consider the whole neurovascular unit rather than the brain endothelium as an isolated structure.

The neurovascular unit. The cerebral endothelium is a very dense network of intercommunicating capillaries and microvessels, composed of specialized endothelial cells (**Fig. 1**). BBB endothelium is characterized by the presence of tight junctions (TJs). In addition, cerebral microvascular endothelial cells are surrounded by pericytes, which are important for the maintenance of vascular homeostasis and are source of adult pluripotent stem cells.[10] Finally, basal lamina surrounds the microvessels and astrocytic end-feet sheath the vascular structure. The importance of astrocyte was for long undermined: their role was purportedly limited to providing trophic, metabolic, and structural support for neural networks. Since, it has been demonstrated that astrocytes also play a signaling role: they communicate with neurons via Ca^{2+} signaling, and can release signaling transmitters, termed gliotransmitters.[11]

Functions and characteristics of the BBB. The neurovascular unit acts, besides other roles, as a physical barrier for the CNS. Cerebral endothelium is continuous without any fenestration and intercellular junction complexes are formed. Junction complexes comprise adherens and tight junctions; these are accumulated close to the apical side of endothelial cells.[12] Adherens junctions are composed of cadherin-catenin complexes, and are important in the initiation, maturation and maintenance of endothelial intercellular contacts. TJs are mainly composed of three transmembrane proteins (claudins, occludin, and Junction Adhesion Molecules) associated with cytoplasmic accessory proteins (Zonula Occludens-1, -2, -3, cingulin). These latter link membrane proteins to the actin cytskeleton, which is involved in the structural and functional integrity of cerebral endothelium.[12,13]

This typical angioarchitecture, with junction complexes that fasten together adjacent endothelial cells,[14] together with minimal vesicular transport activity in the endothelial cells,[9,14] explain mostly the restrictiveness of the BBB. As passive diffusion between the bloodstream and the brain is abolished, BBB strictly controls nutrient transport to the brain as well as efflux of metabolites.[15] Moreover, BBB confers a large protection against toxicity of many xenobiotics, as it regulates efflux of drugs from the CNS to the blood.[16] Finally it is a good protection against pathogens: it restricts the entry of circulating immune cells[17] and pathogens.[18] Retroviruses, as other viruses, have developed different ways to overcome this protective barrier, as described as follows.

Blood-Brain Barrier, HIV and Other Lentiviral Infections

HIV-infected patients commonly develop neurological symptoms, such as HIV-associated dementia (HAD), and its pathological correlate, HIV-encephalitis (HIVE). These can occur even in the absence of opportunistic infections and are characterized by motor and cognitive disorders, such as limb muscle weakness, loss of memory, depression and dementia.[19,20] The clinical manifestations are accompanied by histological hallmarks, such as neocortical and subcortical damage within the white and gray matter,[21-23] presence of multinucleated giant cells, neuronal loss and astrocytosis. Although the introduction of highly active antiretroviral therapy (HAART) has been able to reverse some of the clinical manifestations, pathological alterations persist within the CNS of infected patients as the drugs hardly penetrate the CNS turning difficult the control of HIV replication within the brain.[24]

Blood-brain barrier alterations during HIV infection. Blood-brain barrier functional perturbations have been early identified

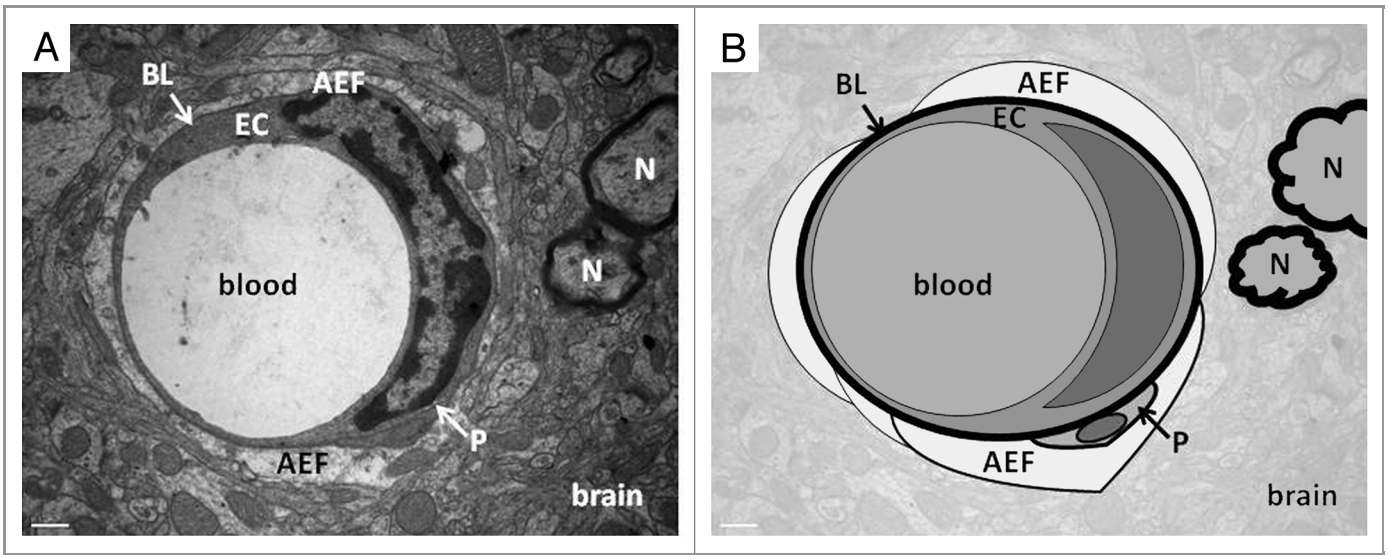

Figure 1. Transmission electron microscopy (A) and schematic view (B) of rat brain illustrating the neurovascular unit. This complex includes microvessel endothelial cells (EC), based on basal lamina (BL), astrocytes end-feet (AEF) and some neurons (N) in the vicinity. Scale bar: 0.5 μm.

during HIV infection, as shown by the presence of cellular infiltrates and diffusion of seric markers within the brain parenchyma,[24-27] as well as by dynamic magnetic resonance imaging.[28] Additional evidence of BBB alteration in the CNS of infected patients has been brought by observation of TJ disorganization, especially in the expression pattern of occludin and the protein Zonula Occludens 1 (ZO-1).[29] Interestingly, whereas brain sections from HIV infected patients without HIVE showed normal amounts of occludin- or ZO-1-reactive blood vessels, brain sections from patients with HIVE showed marked alterations in both the intensity and staining pattern of occludin and ZO-1.[29] Moreover, a correlation could be established between the level of ZO-1 disorganization in brain endothelia and the extent of dementia in HAD patients.[30]

Three main mechanisms were proposed to explain BBB alteration during HIV infection: (1) BBB is altered in response to proinflammatory cytokines secretion by HIV-infected cells or activated endothelial cells, (2) BBB is altered in response to secreted viral proteins (Tat or gp120) and (3) BBB is altered upon infection of endothelial cells by HIV.

Effect of proinflammatory cytokines secretion. During the asymptomatic phase, HIV-infected patients exhibit a chronic activation of immune system, accompanied by dysregulation of cytokine secretion.[31,32] At this stage, HIV can be detected in the CSF,[33] as the consequence of trafficking of either activated and infected CD^{4+} T cells, monocytes or dendritic cells from the periphery. After the virus has reached the CNS, productive virus replication occurs in the CNS, which is accompanied by massive cytokine and chemokine secretion in the CNS.[34,35] Cerebral endothelial cell functions are deeply impaired during this chronic activation; they overexpress cell adhesion markers such as intercellular adhesion molecule-1 (ICAM-1) and secrete metalloproteases, which induce basal lamina thinning.[36-38] This facilitates mononucleated cells extravasation into the CNS.

Effect of secreted viral proteins. Since clinical manifestations of HIV infection often do not correlate directly with viral titers, it has been thought that the effects of infection could be mediated by viral soluble factors secreted from HIV-infected cells.

Among them, the viral Tat protein, which is secreted by infected cells[39] and is able to cross cell membranes, can be detected in both sera and CSFs from HIV-infected patients.[40] Evidence of a deleterious effect of Tat on BBB has been brought both on cellular models in vitro and in vivo.[41-45] Tax-induced BBB alteration occurs through the disorganization of TJs in vitro: decrease in claudin-1, claudin-5 and ZO-2 expression were observed in cellular models treated with recombinant Tat.[44] Moreover, in vivo, exposure to recombinant Tat were sufficient to induce redistribution of claudin-5 immunoreactivity in a murine model.[44] Similarly, Tat administration into the brain hippocampi of C57BL/6 mice resulted in decreased mRNA levels of ZO-1 and drastic reduction of ZO-1 continuity in brain microvessels.[43] Such changes are mediated by the activation of extracellular signal-regulated kinase 1/2 (ERK1/2), suggesting that Tat-induced oxidative stress may play an important role in affecting BBB integrity via the ERK1/2 pathway. In fact, a dose-dependence relationship was established between the oxidative stress degree and Tat concentration in brain endothelial cell cultures.[45] Via the increase in oxidative stress, HIV infection could increase cytoplasmic calcium concentration, thus altering mitochondrial functions and inducing endothelial cell apoptosis. Endothelial cell apoptosis was indeed observed in the brains of some AIDS patients[46]; however the importance of such a mechanism has not yet been established in vivo.[47]

The HIV envelope glycoprotein gp120 could also alter BBB integrity. Alterations in the BBB have been detected in transgenic mice expressing solely the viral gp120. Gp120 expression induces matrix metalloproteinase-2 secretion in vivo that might alter the basal lamina,[37] oxydative stress[48] and ZO-1 and occludin degradation accompanied with claudins expression alterations.[49] TJ proteins degradation might be mediated by proteasome in cultured human brain microvascular endothelial cells.[50] Eventually, BBB permeability is impaired and infected monocytes migration increased.[51]

Direct infection of endothelial cells by HIV. Brain endothelial cells can potentially be infected. Microvascular cerebral endothelial cells express HIV receptor and co-receptors.[52,53] Moreover, primary endothelial cells can be productively infected by HIV in vitro,[54,55] although such an infection could only been demonstrated for dual-tropic X4R5 HIV strains. Infection of brain endothelial cells could have many deleterious effects on BBB integrity: (1) HIV-infected endothelial cells could secrete cytokines and the viral protein Tat, with deleterious effect on BBB; (2) infection of brain endothelial cells enter apoptosis; (3) infected endothelial cells could secrete metalloproteases able to alter BBB.[56]

Infection of brain endothelial cells in vivo is still a matter of debate. Some reports suggested the presence of infected endothelial cells through in situ hybridization experiments.[57-59] However, these studies could not exclude that such positive signal could correspond to infected perivascular macrophages, in fact they concluded solely based on morphological criteria, in the absence of endothelial cell typing by histochemistry. In addition, using PCR/in situ hybridization technique, no HIV-infected endothelial cells could be detected in the brains of adult patients with AIDS, including patients with HAD.[60]

Cell trafficking through BBB during HIV infection. In addition to altering BBB functions either by viral-induced TJ disorganization or endothelial cell cytopathic effect, HIV can access the CNS by an increased trafficking of HIV-infected CD^{4+} T cells or circulating monocytes; this is named the "Trojan horse" mechanism.[61]

Whereas in healthy individuals leukocyte trafficking toward the CNS is very low, in inflammatory conditions lymphocytes and monocytes/macrophages gain access to the CNS by increased migration through the BBB.[17,62] In the case of HIV infection, inflammation in the CNS, and subsequent increased transmigration of lymphocytes and monocytes through the BBB, have been shown (for a recent review, see ref. 63). For example, Tat induces adhesion molecules in endothelial cells and chemokines secretion by astrocytes and microglial cells, thus possibly enhancing leukocyte trafficking toward CNS.[64] In addition, the viral protein gp120, which can be detected in the brain of HIV-1 infected

patients,[65] triggers the release of MCP-1, as a potent chemoattractant for monocytes.[66] Interestingly, an increased risk of HAD has been shown to be linked to a mutant MCP-1 allele.[67] Finally, proinflammatory cytokines levels are elevated in CSF and brain parechyma of HAD patients. These can alter BBB integrity, increase the expression of the adhesion molecules ICAM-1, Vascular Cell Adhesion Molecule-1 (VCAM-1) and E-selectins on endothelial cells, thus facilitating leukocyte adhesion, rolling and estravasation into the brain.[68]

Interestingly, some hypothesized that the increased trafficking of leukocytes toward the CNS during HAD would be a consequence of early alteration of the gastrointestinal mucosa observed during HIV infection.[69] In fact, gastrointestinal rupture could lead to translocation of bacterial endotoxin LPS, which could induce a generalized systemic activation, LPS-induced BBB damage[70] and an increase in monocyte transmigration.[71,72]

Blood-brain barrier and other lentiviruses. Most of the observations reported for HIV seem to stand true for other lentivirus-associated CNS disorders.

As for its human counterpart, the simian immunodeficiency virus can induce encephalitis in macaques.[73-76] Brains of SIV-infected macaques exhibit fragmented and reduced immunoreactivity for occludin and ZO-1, in association with accumulation of perivascular macrophages.[77]

Upon Feline Immunodeficiency Virus (FIV) infection, BBB and choroid plexus functions are impaired.[78] In vitro, cat brain microvascular endothelial cells can be infected with FIV, which could lead to important alterations of BBB functions.[79] However, as for HIV-1, FIV-infection of brain endothelial cells in vivo remains controversial; the current model favors a CNS invasion by FIV through trafficking of infected lymphocytes.[80]

Interestingly, both Visna virus and Caprine Arthritis Encephalitis virus can cross the BBB, but since no free virus could be detected in the blood, it has been suggested once again that the major entry mechanism for lentiviruses is the "Trojan horse" mechanism.[81,82]

Blood-Brain Barrier and HTLV-1

Human T-cell leukemia virus type 1 (HTLV-1), a retrovirus that infects 15 to 20 millions people worldwide, is known to cause a variety of diseases, including a chronic neurological syndrome called either tropical spastic paraparesis or HTLV-1-associated myelopathy (TSP/HAM).[83-85] TSP/HAM is a slowly progressive neurological disease, which occurs in less than 3% of HTLV-1 infected people, and is characterized by BBB alterations such as immunoglobulin and fibrinogen deposit in the brain parenchyma,[86,87] and crossing of HTLV-1 infected lymphocytes through the BBB.[88,89]

Three putative mechanisms have been proposed for TSP/HAM pathogenesis. First, the "bystander" model is based on the observation that CSF from HAM/TSP patients is enriched in pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-6 and interferon-γ (IFN-γ).[90-92] These pro-inflammatory cytokines, as well as HTLV-1 proteins (such as the viral transactivator Tax protein) are secreted by infiltrating infected lymphocytes that have crossed the BBB and could induce glial cell stress and effect on myelin.[93] In the second model, called the "cytotoxic model," glial cells get infected by HTLV-1.[94] Infected glial cells would then be recognized as targets by anti-HTLV-1 cytotoxic lymphocytes (CTL) and subsequently lysed. The third model puts at play an auto-immune mechanism. The viral Tax protein dominant epitope (346–353) cross-reacts with a neuron-specific ribonucleoprotein, hnRNP A1.[95] Therefore, the humoral immunity against HTLV-1 can give rise to antibodies directed against neuronal antigens,[96] and such antibodies have been detected in sera from TSP/HAM patients.

All hypotheses include an initial step of BBB breakdown and/or BBB crossing by HTLV-1 infected lymphocytes. In this context, in vitro and ex vivo studies have been performed to decipher the cellular and molecular mechanisms of BBB alteration and HTLV-1 infected lymphocytes crossing through this latter. In an in vitro rat endothelial model, HTLV-1 infected lymphocytes could alter the endothelial monolayer through TNF-α secretion, and HTLV-1 virions could be transferred through endothelial cells, either by transcytosis or transient infection.[97] More recently, in an in vitro model of human brain endothelial cells, HTLV-1 infected lymphocytes were able to alter TJ structures, increase paracellular permeability and transcellular migration, via secretion of both IL-1α and TNF-α.[98] These two cytokines have also been shown in an in vitro model of epithelial choroid cells to be able to mediate the alteration of epithelial transport processes induced by HTLV-1 infected lymphocytes.[99] In addition, cerebral endothelial cells can be infected by HTLV-1, as shown in vitro, in human brain endothelial cells, and in necropsy spinal cord sections from TSP/HAM patients.[100] In vitro, such an infection is productive and alters BBB functions, thus providing additional mechanisms for BBB alteration and viral access to the CNS during TSP/HAM (**Fig. 2**).

Conclusion and Perspectives

In conclusion, although the pathological consequences are rather different, the two human retroviruses linked to neurological symptoms, i.e., HIV and HTLV-1, bypass and alter the BBB using very similar mechanisms. Besides the "Trojan horse" strategy to invade the CNS via infected infiltrating cells, the role of the infection of endothelial cells remains to be further investigated. BBB alterations that occur during retroviral infection are often related with a combination of viral-induced proinflammatory cytokines secretion and direct effect of viral proteins (Tat or Tax).

However, the interactions between retroviruses and BBB might have to be revisited in the context of both anti-retroviral therapy and social behaviors, such as drug abuse. Concerning HTLV-1, the use of valproate, a drug often use for epilepsy treatment, has been shown to increase the proviral load and alter motor functions at the beginning of the treatment.[101] Concerning HIV, the introduction of highly anti-retroviral therapy (HAART) has drastically limited BBB alterations, which were previously frequently detected.[102] Indeed, HAART has been shown to limit or prevent lymphocytic infiltration toward the CNS. However,

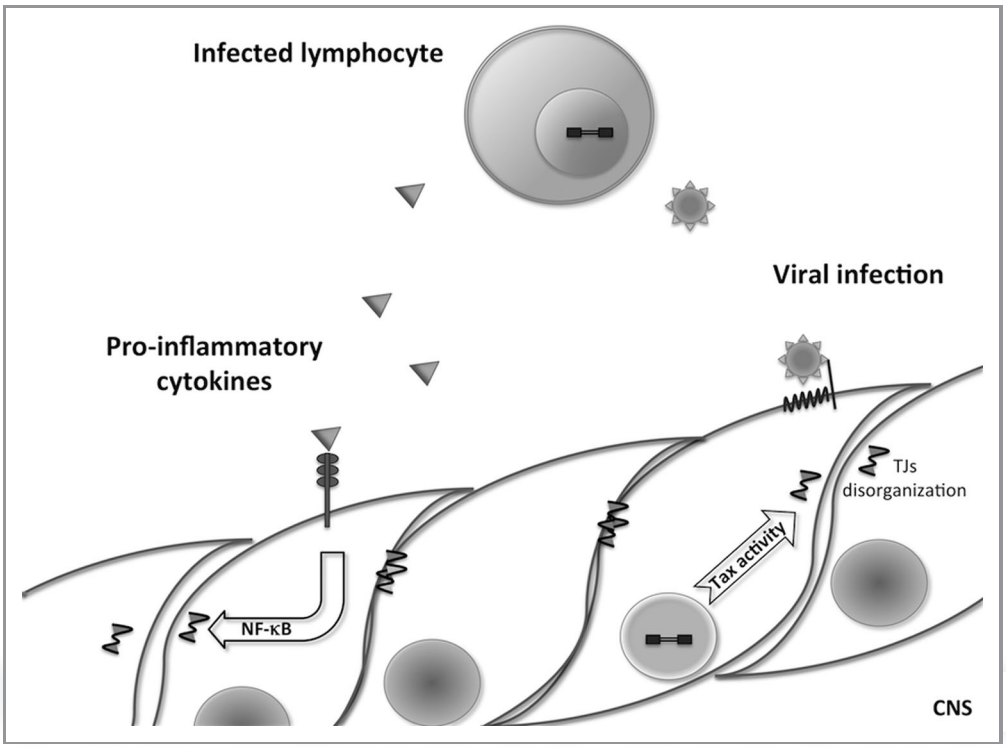

Figure 2. Possible mechanisms of blood-brain barrier disruption by HTLV-1-infected lymphocytes. During TSP/HAM, HTLV-1 infected lymphocytes may disrupt the blood-brain barrier either by proinflammatory cytokine secretion (TNF-α, IL-1α) that activate NFκB pathway in endothelial cells, which induce tight junction disruption, or by infecting endothelial cells; the viral protein Tax could then induce tight junction disorganization.

during the occasional immune reconstitution inflammatory syndrome (IRIS) associated with HAART, a massive lymphocyte extravasation through brain parenchyma has been reported.[103] The mechanisms of BBB alteration in this context might be different. In the context of drug abuse, the viral capacity to penetrate the CNS might be modified. As an example, methamphetamines alter BBB permeability through modulation of TJ expression,[104] facilitating the entry of the virus or infected cells. In the same manner, use of cocaine can increase HIV-1 neuroinvasion by upregulating the expression of adhesion molecules and matrix metalloproteinases in cultured brain microvascular cells.[105,106] The viral protein Tat effects on BBB integrity are also directly exacerbated by cocaine, with a differential effect between the Tat proteins from HIV-1 clades B and C.[107] By contrast, cannabinoids can inhibit HIV-1 gp120-induced alterations in cultured microvascular endothelial cells.[108] Finally, since combination of HAART (and especially the HIV protease inhibitor saquinavir) with chronic exposure to nicotine has been recently shown to induce BBB integrity alteration[109,110]it makes clear that retrovirus interaction with the BBB remains a topic of major interest in the next years.

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